SALVAGE HYPERTHERMIC GEMCITABINE AND DOCETAXEL COMBINATION CHEMOTHERAPY AFTER BCG FAILURE IN NON-MUSCLE INVASIVE BLADDER CANCER PATIENTS

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ABSTRACT

Background: In patients with non-muscle invasive bladder cancer (NMIBC), intravesical BCG has been shown to reduce the rate of disease recurrence and disease progression, as well as improve disease-specific survival. While Bacillus Calmette-Guerin (BCG) has become the gold-standard therapy for NMIBC, there are still patients who fail this therapy or are not good candidates for it. Although a radical cystectomy is recommended when BCG is failed, some patients either desire bladder preservation or are not surgical candidates. Thus, further exploration into salvage chemo therapy treatments should be done to provide these patients with an alternative treatment option.

Objective: The purpose of this study is to analyze if combination Gemcitabine and Docetaxel chemotherapy (GEM/DOCE) is a successful salvage option in adults who have failed or cannot tolerate BCG therapy for NMIBC, and are poor surgical candidates for a radical cystectomy (RC) or desire bladder preservation.

Methods: 60 patients who received GEM/DOCE between 2007-2017 were identified and characterized (51 were classified as BCG failure and 9 were BCG naïve). Patients were treated with 6 weekly instillations of Gemcitabine (200 mg/10 mL) followed immediately by Docetaxel (20 mg/10 mL). This study measured overall treatment success, defined as no bladder cancer recurrence, no progression to muscle invasion or metastasis, no cystectomy, and no death due to bladder cancer. Kaplan Meier curves were used to ascertain probability of treatment success in patients. The log rank test was used to identify factors associated with treatment success.

Results: Sixty patients received treatment with a median follow-up of 14.9 months. All of the patients completed the induction course with no significant adverse effects. Overall treatment success was 83% (50/60) at first surveillance, 69% at 1 year, and 55% at 2 years after induction of GEM/DOCE in the entire cohort, and 90% (53/51) at first surveillance, 74% at 1 year, and 56% at 2 years in the BCG-failure patients. Patients who underwent more total GEM/DOCE instillations (induction + maintenance) were less likely to recur. All-cause and bladder-cancer-specific survival were 97.9% at 1 year. At 2 years, all-cause and bladder-cancer-specific survival were 85.9% and

94.6% respectively. Three patients underwent cystectomy at a median of 10.2 months (2 secondary to recurrences). In the entire cohort, 3 (5%) patients who completed GEM/DOCE underwent progression of their disease.

Conclusions: Hyperthermic GEM/DOCE seems to be a well-tolerated salvage regimen that demonstrates a reasonable efficacy and meets the criteria for new therapies for NMIBC set by the FDA and AUA in 2014. As such, it warrants further investigation in a prospective, controlled manner to optimize a protocol for patients who remain a challenge to treat after they fail or are not candidates for BCG and do not want a RC.

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INTRODUCTION

Bladder cancer has the sixth highest incidence rate of all cancers in The United States. When looking specifically at males in the country, this incidence rate goes up to the fourth highest of all cancers.[1] Of the patients newly diagnosed with bladder cancer, approximately 75% have disease confined to the urothelium (stage Ta, CIS) or submucosa (stage T1), also referred to in this thesis as non-muscle invasive bladder cancer (NMIBC).[2] Current guidelines state that disease management of NMIBC should include a transurethral resection of all bladder tumors (TURBT) (with repeat resection in T1 disease), followed by intravesical Bacillus Calmette-Guérin (BCG) immunotherapy for intermediate and high-risk tumor patients.[2–4] Intravesical BCG has been shown to reduce the rate of disease recurrence and disease progression, as well as improve disease-specific survival.[5,6]

Despite being the gold standard treatment, up to 40% of individuals with NMIBC won't respond to intravesical BCG therapy[7] and up to 75% of individuals will develop a new tumor within 5 years.[8] The latest European Association of Urology (EAU) guidelines state that patients facing BCG failure are unlikely to respond to further therapy with BCG. Although the guidelines acknowledge various bladder preservation options in the setting of BCG failure, they classify them as oncologically inferior and present radical cystectomy (RC) as the preferred option.[2,7,9] A clinically meaningful oncologic benefit for patients failing or recurring post BCG has been defined by expert consensus as an initial complete response rate (for carcinoma in situ) or recurrence-free rate (for papillary tumors) of at least 50% at 6 months, 30% at 12 months, and 25% at 18 months.[10] Even though RC is the recommended treatment option in the setting of BCG failure, many patients prefer bladder preservation after considering the potential morbidity and mortality associated with RC[11], while others are not surgical candidates for various reasons. In this situation, salvage intravesical treatments have become an important option for patients.

In an effort to provide an additional salvage treatment option, a dose-dense, hyperthermic, combination Gemcitabine and Docetaxel chemotherapy treatment (GEM/DOCE) has been offered to patients with NMIBC who failed BCG but sought an alternative to RC. Gemcitabine is a cytotoxic chemotherapeutic agent, which works by inhibiting DNA synthesis. Gemcitabine is

given to patients with bladder cancer as part of a chemotherapy treatment regimen, and has thus far been relatively well tolerated.[12] Gemcitabine was also shown to be a viable treatment option in NMIBC BCG refractory patients in a Phase II trial. 30 patients were given two courses of twice weekly 2,000 mg/100 mL Gemcitabine therapy for three weeks with a median follow-up of 19 months. Of the 30 patients, 15 (50%) patients had a complete response. Of these complete-responders, the 1-year recurrence-free survival rate was 21%.[12] In a subsequent, multi-center Phase II trial, 58 NMIBC patients who had failed at least 2 courses of BCG were treated with a 6-week induction course of 2,000 mg/100 mL Gemcitabine therapy and then followed with maintenance therapy for a year. The 1-year recurrence-free survival rates for patients with a complete response to the treatment was 28%, and the 2-year recurrence-free survival rate was 21%.[13] In another prospective study, 20 NMIBC BCG refractory patients were given a more concentrated dose of 2,000 mg/50 ml Gemcitabine for 6 weeks, and then followed with maintenance therapy for 12 months. At 15.2 months, 45% of the patients were still disease free and 5 patients experienced progression.[14] Overall, these results indicate that Gemcitabine can be effective in some patients with BCG refractory bladder cancer, and should be further explored and offered to patients who are not candidates for or refuse radical cystectomy.

Docetaxel is a cytotoxic chemotherapeutic agent, which works by promoting intracellular bundling of microtubules. This results in cell cycle inhibition during the M-stage and subsequent cell death. Docetaxel has been shown to have anti-tumor properties in a wide range of cancers, including bladder cancer (urothelial carcinoma).[15] In one study, patients who failed BCG were given salvage intravesical Docetaxel therapy with a maximum dose of 75 mg/100 ml. The 1 and 2-year recurrence-free survival rates were 45% and 32% respectively.[16] Another study compared only initial induction therapy to induction therapy with maintenance therapy of Docetaxel in NMIBC BCG refractory patients. The doses varied between patients, but the maximum dose used was 75 mg/100 ml. The results showed that median time to recurrence in initial responders treated with and without Docetaxel maintenance therapy was 39.3 vs 19.0 months respectively.[17] This shows that with docetaxel maintenance therapy, the time to recurrence is prolonged. Docetaxel therapy has been shown to have even higher efficacy when combined with other chemotherapeutic agents.[15,18]

In 2015, Steinberg et al. published the first study of sequential GEM/DOCE for NMIBC patients who failed BCG therapy; a total of 45 patients were included. They demonstrated a disease free survival (DFS) rate of 54% at 1 year and 34% at 2 years.[18] Milbar et al. published a similar study in 2017 with 33 patients utilizing the same chemotherapy protocol as Steinberg et al. and demonstrated a DFS rate of 42% at 1 year and 24% at 2 years, while survival free from high-grade recurrence was 56% at 1 year and 42% at 2 years.[19]

Although in 2007 we began offering a similar intravesical chemotherapy protocol, our regimen varies in a few ways. Specifically, our Docetaxel dose is almost three times as concentrated as that used by Steinberg et al. and Milbar et al., and both the Gemcitabine and Docetaxel are administered in a smaller volume. Furthermore, our protocol calls for warming both chemotherapeutic agents prior to instillation, as hyperthermia has shown to improve bladder preservation rates.[20] In a systematic review looking at intravesical Mitomycin-C (MMC) and hyperthermia, the results showed a 59% relative reduction in NMIBC recurrence with chemohyperthermia than with MMC alone.[20]

The purpose of this study is to answer the question, in adults who have failed BCG therapy for non-muscle invasive bladder cancer and are poor surgical candidates for radical cystectomy or desire bladder preservation, is combination Gemcitabine and Docetaxel chemotherapy a successful salvage option? This study is a retrospective review of patients who have failed or could not tolerate BCG therapy for NMIBC and opted to receive concentrated intravesical hyperthermic GEM/DOCE at BCG Oncology. Treatment success is defined as no bladder cancer recurrence, no progression to muscle invasion or metastasis, no cystectomy, and no death due to bladder cancer.

MATERIALS AND METHODS

Study population and design

After Institutional Review Board approval was received, patients who received concentrated intravesical, hyperthermic, GEM/DOCE between 2007-2017 at our institution were identified (*n*=60) and retrospectively reviewed.

This study measured overall treatment success, defined as no bladder cancer recurrence, no progression to muscle invasion or metastasis, no cystectomy, and no death due to bladder cancer. Time to recurrence, all-cause and bladder-cancer-specific survival rates were also measured. The study also looked at any complications or side effects that occurred as a result of the chemotherapy. Exclusion criteria included lack of significant follow-up and receiving alternative intravesical agents during the course of treatment. Significant follow-up was defined as having a 3-month cystoscopy to assess response, and subsequent clinic visits to assess progress.

Study variables

The following variables were collected from patients' medical records: gender, age at time of GEM/DOCE induction, race, smoking status, all pathology reports (grade and stage of the cancer) pre-induction, start and end date of BCG therapy, start date of chemotherapy protocol, number of chemotherapy treatments and dosages, any follow-up pathology reports, number of recurrences before and after care at BCG Oncology, side effects of treatment, date of cystectomy if relevant, and date/reason for mortality.

Gemcitabine/Docetaxel intravesical treatment protocol

For induction, patients receive 6 weekly instillations of the combination intravesical chemotherapy (1 instillation a week for 6 weeks). Patients are mildly dehydrated overnight and take sodium bicarbonate (in the form of Alka-Seltzer tablets, 2 tablets the night before the procedure and 2 tablets the morning of the procedure) to alkalinize the urine. They are asked to refrain from drinking any liquids 4 hours before the treatment. Water diluent is warmed to 43-

45°C (a microwave or coffee warmer can be used to heat a water bath in which the water to be used to dilute the drugs are placed). The bladder is carefully drained with a Foley catheter, and the Foley balloon is filled with 20-40 mL (depending on bladder capacity) of warm water. 200 mg Gemcitabine in 10 mL of warm water is instilled and the catheter clamped. With the small volume used, air is used to chase the drug and ensure it is all instilled. Balloon water is exchanged with warm water every 20 minutes as patients are rotated from front to back, and side to side. After one hour, the Gemcitabine is emptied and 20 mg of Docetaxel in 10 mL of warm water is instilled and retained for two hours with the patients once again rotating. The drug order is important.

Maintenance consists of 3 weekly treatments of the combination chemotherapy at 3 months, 6 months, and 9 months. Each maintenance course follows cystoscopy, and can be done on the same day.

Surveillance

Cystoscopies are performed every 3 months up until 2 years after treatment induction. Afterwards, the cystoscopies are spaced to every 6 months. Bladder washings with cytology are performed with every cystoscopy. If the cytology comes back as malignant or there is a visible tumor on cystoscopy, the patient has developed a recurrence of their cancer.

Statistical analysis

Data was retrospectively collected and stored in a deidentified database. Univariate Cox regression was performed to evaluate for any clinical predictors of recurrence. Kaplan Meier curves were used to ascertain probability of treatment success in patients categorized by pre-treatment grade (CIS, HG, LG), classification of BCG failure, number of prior BCG induction courses, and number of positive pre-treatment bladder pathology samples. The log rank test was used to identify statistical differences between these respective groups. The above statistical protocols were used to analyze all-cause survival and bladder-cancer-specific survival as well.

RESULTS

Cohort demographics

The 60-patient cohort had a median age at treatment of 73 years (range 48-88) (Table 1). Nine (15%) patients in the cohort were BCG naïve, of whom 6 patients were transplant recipients and immunosuppressed. The remaining 51 patients failed previous BCG therapy. Patients with a BCG failure were further classified by their sub-types like BCG intolerant (disease recurrence after a less than adequate course of therapy is applied due to a serious adverse event or symptomatic intolerance), BCG relapsing (recurrence of disease after achieving a disease-free status by 6 months), or BCG refractory (rapidly recurrent or progressive disease noted at 3 months after diagnosis or persistent disease at 6 months after diagnosis in light of 2 BCG induction courses or induction plus maintenance).[18] Four (7%) patients in the cohort were BCG intolerant, 24 (40%) patients were BCG relapsing, 19 (32%) patients were BCG refractory, and 4 (7%) patients failed BCG but could not be categorized further based on the available information from previous records. The median number of prior BCG induction and maintenance courses are 1 (range 0–3) and 1 (range 0–6) respectively.

Treatment tolerance

Thirty-one patients (52%) reported experiencing adverse symptoms during their BCG treatment course, but only 10 of these patients had symptoms that impacted the treatment schedule with short 1-week delays. All the patients were still able to finish their treatment course. The most common side effects noted were mild fatigue (20%), hematuria (20%), mild urinary frequency/urgency (13%), dysuria (10%), and nocturia (7%).

Table 1. Demographics of patients who received combination Gemcitabine and Docetaxel for NMIBC

Variables	N=60
Age at GEM/DOCE induction (median, range)	73 (48-88)
Gender (male, %)	47 (68.1)
Race (Caucasian, %)	54 (90.0)
Marital Status (Married, %)	48 (80.0)
Smoking Status (yes, %)	42 (70.0)
Packs of cigarettes per year (median, range)	30 (1-120)
Number of BCG Induction Courses (median, range)	1 (0-3)
Number of Total BCG Maintenance Courses (median, SD)	1 (0-6)
Number of Positive Prior Bladder Pathology (n, %)	
1	5 (8.3)
2	14 (20.3)
3	22 (36.7)
>3	19 (31.7)
BGC Status (n, %)	
BCG Refractory	19 (31.6)
BCG Relapse	24 (40.0)
BCG Intolerant	4 (6.7)
BCG Naive	9 (15.0)

Treatment success

Overall treatment success was 83% (50/60) at first surveillance, 69% at 1 year, and 55% at 2 years after induction of GEM/DOCE (Figure 1). The overall median follow-up for the cohort was 14.9 months (range 1.9–89.4 months). In those who failed therapy (n=21, 20 recurrence, 1 cystectomy not related to recurrence), median time to failure was 6.1 months (range 2.4–21.4 months). Treatment success in those who failed BCG therapy (cohort minus BCG naïve) was 88% (45/51) at first surveillance, 74% at 1 year, and 56% at 2 years after induction of GEM/DOCE (Figure 2). There was no statistically significant difference in treatment success when the treatment failure group was stratified by pre-chemo stage/grade, BCG failure type, number of prior BCG induction courses, or number of positive prior bladder (Figure 3).

Figure 1. Kaplan-Meier plot of treatment success with GEM/DOCE in patients with NMIBC (n=60)

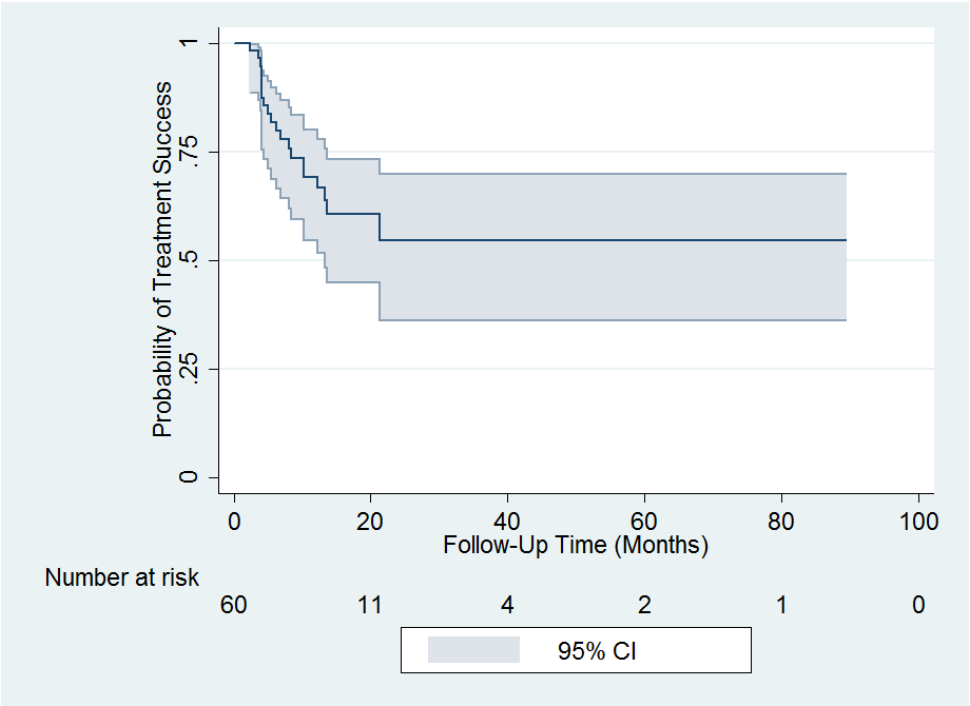


Figure 2. Kaplan-Meier plot of treatment success with GEM/DOCE in patients with NMIBC who failed BCG therapy (n=51)

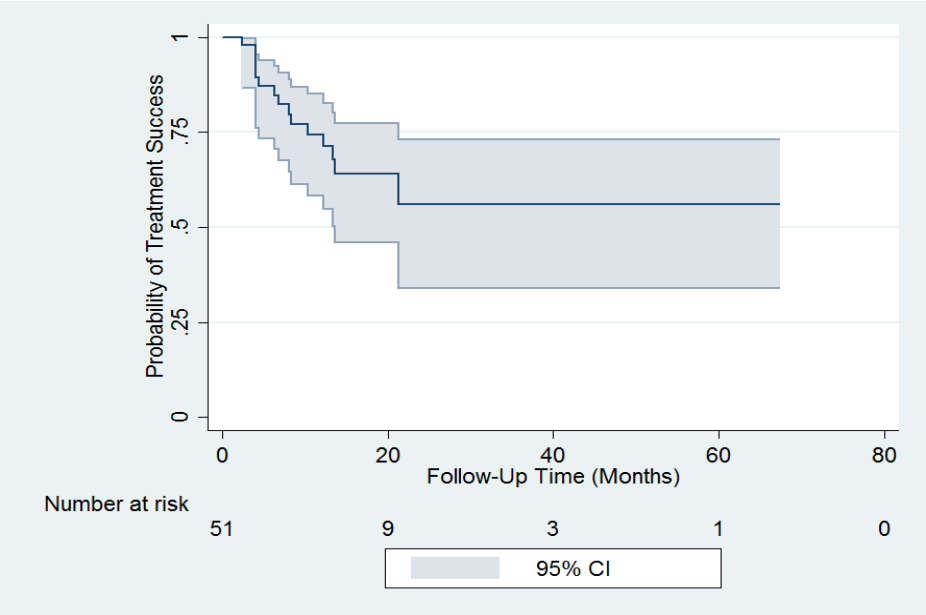
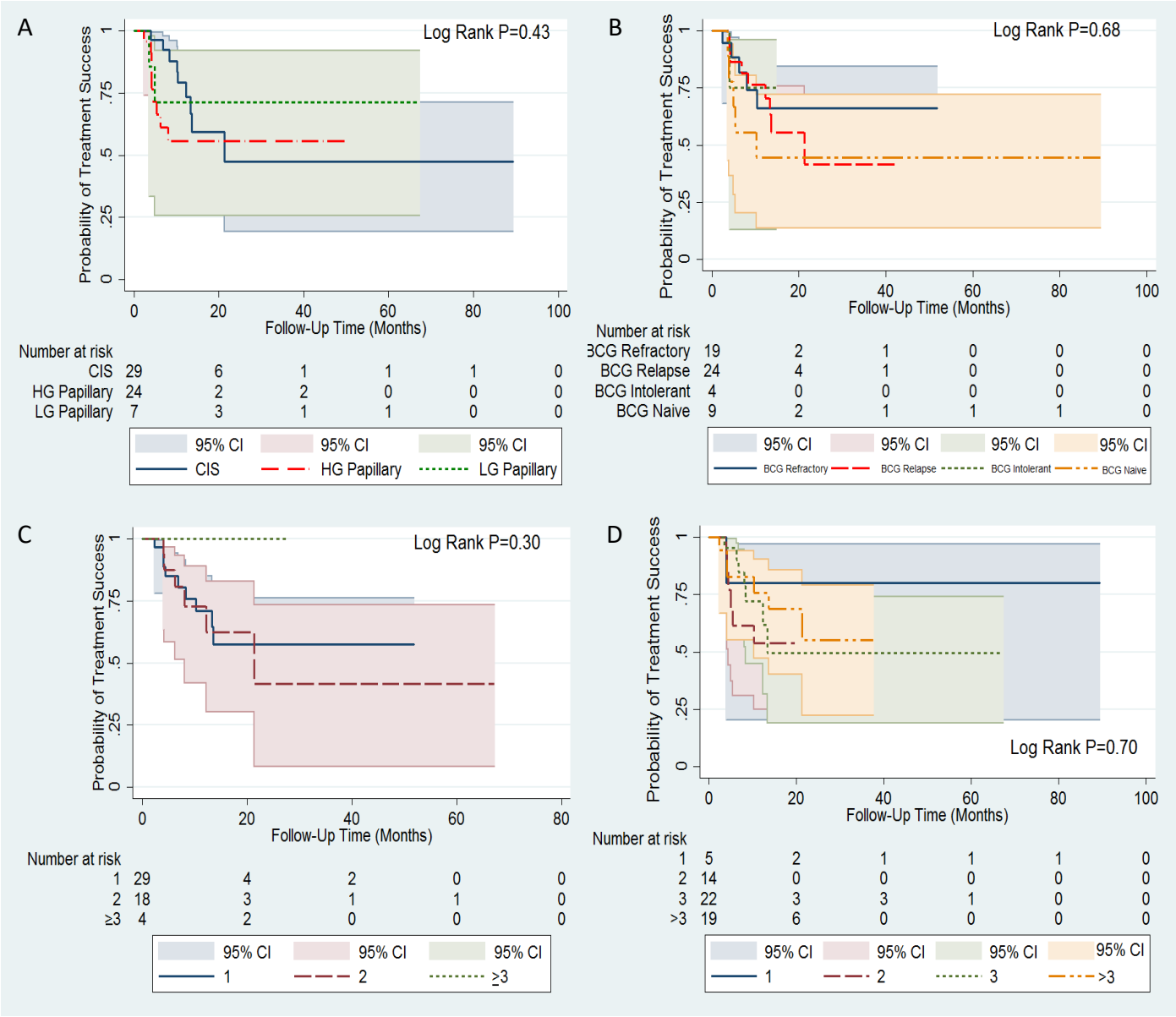


Figure 3. Kaplan-Meier plots of treatment success with GEM/DOCE in patients with NMIBC stratified by A) Pre-chemo stage/grade; B) Type of BCG failure; C) Number of prior BCG failures; and D) Number of prior positive NMIBC bladder pathologies



Clinical predictors of recurrence

In order to identify clinical predictors of recurrence after GEM/DOCE treatment, patients were stratified by recurrence and their baseline characteristics were analyzed (Table 2). A total of 20 patients (33%) had a recurrence of their NMIBC. Patients who underwent more BCG maintenance instillations prior to GEM/DOCE were less likely to recur after receiving GEM/DOCE (p=0.048, HR 0.91). Prior BCG/IFN treatments were also significant (p=0.046, HR 8.64). Lastly patients who underwent more total GEM/DOCE instillations were less likely to recur (p=0.015, HR 0.86). There was no statistical significance noted for age, gender, race, marital status, smoking status, pack-years, number of BCG maintenance courses, other treatments, number of BCG maintenance courses, number of BCG instillations, number of prior positive bladder pathology results, and duration for GEM/DOCE induction. Age (p=0.064) and total number of BCG instillations (0.078) were close to being significant.

Table 2. Characteristics of patients who received GEM/DOCE for NMIBC stratified by recurrence status

Variables	No Recurrence N=40	Yes Recurrence N=20	HR (95% CI)	P-value
Age at GEM/DOCE induction (mean, SD)	74.2 (11.0)	69.6 (7.21)	0.95 (0.91, 1.00)	0.064
Gender (male, %)	32 (80.0)	15 (75.0)	0.58 (0.21, 1.63)	0.31
Race (Caucasian, %)	36 (90.0)	18 (90.0)	1.10 (0.25, 4.79)	0.89
Marital Status (Married, %)	30 (75.0)	18 (90.0)	2.38 (0.55, 10.3)	0.24
Smoking Status (yes, %)	28 (70.0)	14 (70.0)	1.40 (0.53, 3.67)	0.48
Pack-years (mean, SD)	33.2 (27.9)	31.8 (32.2)	0.99 (0.97, 1.02)	0.77
Number of BCG Maintenance Courses (mean, SD)	1.49 (1.78)	0.93 (1.27)	0.76 (0.53, 1.11)	0.16
Number of Total BCG Maintenance Instillations (mean, SD)	**12.9 (5.93)**	**10.5 (4.82)**	**0.91 (0.83, 0.99)**	**0.048**
Prior BCG/IFN Treatments (yes, %)	**1 (2.50)**	**1 (5.00)**	**8.64 (1.03, 71.8)**	**0.046**
Other Prior Treatments (yes, %)	8 (20.0)	4 (20.0)	0.81 (0.26, 2.45)	0.71
Number of Total BCG Maintenance Courses (mean, SD)	1.51 (1.77)	0.93 (1.28)	0.76 (0.53, 1.10)	0.16
Total Number of BCG Instillations (mean, SD)	13.2 (5.95)	10.9 (5.19)	0.92 (0.84, 1.01)	0.078
Number of Positive Prior Bladder Pathology (mean, SD)	3.25 (1.66)	3.35 (2.11)	1.01 (0.79, 1.26)	0.96
Duration for GEM/DOCE Induction (mean, SD)	6.08 (0.65)	6.15 (0.59)	1.19 (0.65, 2.17)	0.56
Number of Total GEM/DOCE Instillations (mean, SD)	**10.8 (3.87)**	**9.55 (3.87)**	**0.86 (0.76, 0.97)**	**0.015**

Cystectomies

Of the 55 potential cystectomy candidates prior to GEM/DOCE, 3 patients underwent cystectomy at a median of 10.2 months (range 6.1–12.3 months) from the time of first GEM/DOCE instillation (Table 3). One patient could not tolerate the dysuria, frequency and nocturia that remained from her initial cancer even after GEM/DOCE induction was completed, and thus chose to undergo a cystectomy. The remaining two patients chose to undergo a cystectomy after they experienced a recurrence.

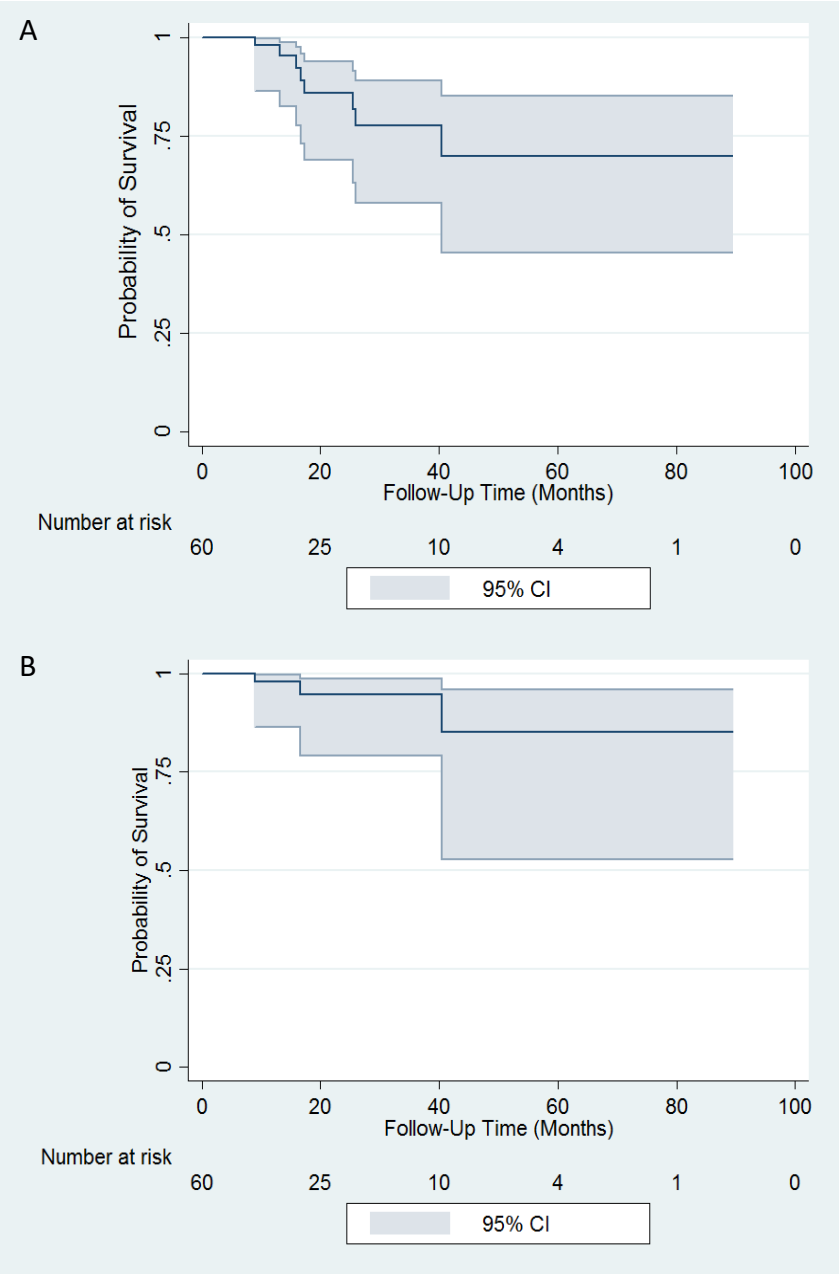
Table 3. Patients treated with GEM/DOCE who underwent a RC

#	Time to cystectomy from GEM/DOCE initiation (months)	Reason for cystectomy	Stage	BCG Failure Type
1	6.1	Lack of improvement in urinary symptoms	T0, N0	BCG Unresponsive
2	10.2	Recurrence	metastatic Progression	BCG Relapsing
3	12.3	Recurrence	Tis, N0	BCG Relapsing

Survival analysis

All-cause and bladder-cancer-specific survival were both 97.9% at 1 year (Figure 4). At 2 years, all-cause and bladder-cancer-specific survival were 85.9% and 94.6% respectively. The first bladder-cancer-specific mortality patient, who was not a cystectomy candidate, was found to have muscle invasive disease 2.4 months after GEM/DOCE initiation, and subsequently passed away 9 months after their GEM/DOCE initiation. The second bladder-cancer-specific patient had a recurrence at 8.3 months after GEM/DOCE initiation, underwent a cystectomy, and subsequently passed away at 16.7 months after their GEM/DOCE initiation. The third and final bladder-cancer-specific mortality patient underwent surveillance for 20 months after GEM/DOCE and was found not to recur, afterwards the patient chose to stop surveillance and eventually passed away at 40.4 months after their GEM/DOCE initiation.

Figure 4. Kaplan Meier plots of A) All-cause survival and B) Bladder-cancer-specific survival in patients with NMIBC treated with GEM/DOCE



DISCUSSION

Patients with NMIBC who fail BCG therapy remain a complicated cohort to treat. Current recommendations by the European Association of Urology (EAU) state that in patients who fail BCG, radical cystectomy (RC) still remains the preferred option. [2,7,9] However, RC has significant risks and comorbidities associated with it.[11] Although Steinberg and Milbar published their studies on GEM/DOCE first, to our knowledge, this is the first study looking at administering GEM/DOCE with an almost 3x concentrated docetaxel dose, while utilizing the benefits of hyperthermia during instillation of the chemotherapy agents. All 60 patients in our study were able to complete the full induction course of GEM/DOCE and none had severe adverse events related to the treatment. This supports the findings of previous GEM/DOCE studies which have found this combination of intravesical chemotherapy to be well-tolerated and relatively safe.[18,19]

Our treatment protocol was successful in 69% of patients at 1 year, which is much higher than the success rates found by Steinberg (54% at 1 year) and Milbar (42% at 1 year).[18,19] The same is true for our success at 2 years of 55%, compared to Steinberg (34% at 2 years) and Milbar (24% at 2 years).[18,19] Our rates were even higher when specifically looking at the BCG failure population with 1-year and 2-year success rates of 74% and 56% respectively.

When compared to other chemotherapeutic agents that have been studied as treatment options for NMIBC, our protocol had higher success rates than those of Mitomycin-C (MMC) which had a 1-year RFS rate of 65% and a 3- year RFS rate of 19%.[21] Additionally, our protocol also had higher success rates when compared to Gemcitabine and MMC combination therapy which had a 1-year RFS rate of 48% and a 2-year RFS rate of 38%.[22]

It is important to note that 3 (5%) patients who completed GEM/DOCE underwent progression of their disease. One patient was found to have progressed to T2 disease and elected for palliative care; he subsequently passed away 9 months after GEM/DOCE initiation. Another patient underwent a cystectomy at 10.2 months after GEM/DOCE initiation, at which time he was found to have metastatic disease and subsequently passed-away at 16.7 months after GEM/DOCE initiation. The last patient with progression was found to have metastatic disease on imaging,

and subsequently passed away at 40.4 months after GEM/DOCE initiation. Despite these risks associated with pursuing salvage chemotherapy, we feel the relatively high success rates of our protocol and the higher quality of life afforded to our patients who were able to avoid RC, both warrant further investigation into GEM/DOCE.

This study is limited by its retrospective design and having no control group to compare the GEM/DOCE results to. Another limitation is the moderate cohort size, which can reduce the power of the statistical analysis. Additionally, the study included 68% men and over 90% Caucasian patients, which is a limited distribution among gender and ethnicity.

FUTURE DIRECTIONS

In 2014, the Food and Drug Administration (FDA) and American Urological Association (AUA) made recommendations that new bladder cancer therapies should have an initial complete response rate of 40%-50% at 6 months and a durable response rate of at least 30% for 18-24 months with the lower bound of the 95% confidence interval (CI) excluding 20% to be clinically meaningful.[23] Our success rates are well above these cutoffs, including the lower bound of our 95% CI at 24 months, which was 36.2%. Thus, we argue further investigation of GEM/DOCE in a prospective, controlled trial is justified and will show promising results. Additionally, considering the current shortages of BCG in the United States, GEM/DOCE could potentially serve as an alternative to BCG therapy in order to prevent delay of treatment.

CONCLUSIONS

In conclusion, hyperthermic GEM/DOCE seems to be a well-tolerated salvage regimen that demonstrates a reasonable efficacy and meets the criteria for new therapies for NMIBC set by the FDA and AUA in 2014. Our results show success rates higher than previously published studies. As such, it warrants further investigation in a prospective, controlled manner to optimize a protocol for patients who remain a challenge to treat after they fail or are not candidates for BCG and do not want a RC.

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